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Evaluation of cardiac and non-cardiac side effects of low dose oxytocin used during caesarean section

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Abstract

Aim: Low-dose administration (<5 units) of oxytocin used in the prophylaxis of postpartum haemorrhage has been recommended because of its haemodynamic side effects. We aimed to analyse the cardiac and non-cardiac side effects of oxytocin, which we prefer to administer 2 units as a low dose, in a large patient population.

Material and Methods: In this observational drug study, patients aged 18-40 years with ASA II physical status scheduled for elective caesarean section under spinal anaesthesia were included. Oxytocin 2 unit intravenous bolus in 5-10 seconds was administered after placenta removal. 23 unit/1000 ml oxytocin infusion was started to be administered within 4 hours after bolus. Cardiac side effects such as hypotension, tachycardia, arrhythmia, T-negativity, ST depression and other adverse effects such as nausea-vomiting, headache, flushing, burning sensation on the face, metallic taste on the tongue after oxytocin bolus were assessed.

Results: The study included 417 patients. Tachycardia was the most common cardiac side effect with a rate of 42.9%, while T-negativity was the least common cardiac side effect with a rate of 1%. Hypotension was observed in 14.6%, chest pain in 10.1% and dyspnea in 5.5%. Headache was the most common non-cardiac side effect (21.6%). The most common type of headache was throbbing (12.5%). Nausea-vomiting occurred in 13.7%, metallic taste on the tongue in 9.4%. 56 patients required methylergonovine. The estimated blood loss was 618.5 ± 326.3 ml.

Discussion: Cardiac and non-cardiac side effects can be seen even with low dose (2 unit) oxytocin administered bolus in 5-10 seconds.

Keywords

Cesarean, Low Dose Oxytocin, Cardiac Effect, Non-Cardiac Effect

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Introduction

Oxytocin is the primary drug used in the prevention and treatment of postpartum haemorrhage [1]. Current guidelines for oxytocin administration during caesarean are diverse, leading to considerable variability in global clinical practice. With unspecified rate and total dose, the World Health Organisation recommends 20 international unit/litre (IU/L) infusion of oxytocin, and the American Academy of Obstetricians and Gynaecologists recommends infusing between 10-40 IU/L. The Royal College of Obstetricians and Gynaecologists recommends that 10 IU oxytocin bolus should be abandoned due to haemodynamic side effects, and instead the bolus dose should be 5 IU and administered slowly [2].

Vascular endothelial cells possess oxytocin receptors. The interaction between oxytocin and the endothelial receptor results in vasodilation through nitric oxide. Vasodilation is the first cardiovascular event that develops after oxytocin use and results in hypotension. Oxytocin causes vasodilatation in peripheral vessels but vasoconstriction in coronary vessels. Chest pain, ST depression and T negativity on ECG may be observed in the patient due to myocardial ischaemia developing as a result of coronary vasospasm. After 2 maternal deaths due to cardiovascular instability were reported with 10 IU bolus of oxytocin, the bolus was reduced to 5 IU [2]. The observation of side effects even in 5 IU bolus applications has led to studies at lower doses. Doses lower than 5 IU have been shown to further reduce hemodynamic side effects without affecting blood loss. In addition, oxytocin may result in nausea-vomiting, headache and flushing. Oxytocin is on the list of 'high alert drugs' due to cardiac and non-cardiac side effects [3].

Despite more than 60 years of use, there is a need for further research and refinement of the use of this agent [3]. There were very few studies in the literature in which a 2 IU bolus was administered [4]. Therefore, we aimed to determine the incidence of side effects of 2 IU bolus oxytocin in a larger patient population.

Material and Methods

The patient was included from December 2020 to April 2022. Informed consent was obtained from all participants. Patients aged 18-40 years, with ASA II physical status, who were planned to undergo caesarean section under spinal anaesthesia under elective conditions were included in this study. Patients who underwent emergency caesarean section or general anaesthesia, had heart disease, pulmonary embolism or chronic respiratory disorders, and ASA > II were excluded. Cases that met the study conditions but failed spinal anaesthesia or returned to general anaesthesia were excluded from the study.

Demographic data, including age, height, weight, body mass index, comorbidities, gestational hypertension, and gestational diabetes mellitus, were collected. Patients were placed in a 15° left lateral tilt position to prevent aortic-caval compression syndrome. Standard monitoring was carried out, including non-invasive blood pressure, pulse oximetry, and electrocardiography. Blood pressure was measured every two minutes. After providing antisepsis, spinal anesthesia was applied with a 25 G Quincke-tipped spinal needle through the L3-L4 or L4-L5 intervertebral space in sitting position. Hyperbaric bupivacaine (%0.5) 9-10 mg and fentanyl 10 mcg was injected intrathecally. Surgery was allowed to start when the sensory block level was T6 dermatome and above. Spinal anesthesia induced hypotension episodes were treated with ephedrine 10 mg. Atropine 0.5 mg was administered when bradycardia developed.

1 IU/1 ml oxytocin was obtained by adding 4 ml isotonic solution to 5 IU/1 ml oxytocin, 2 IU of which was used for bolus administration and the remaining 3 IU was added to the solution containing 20 IU oxytocin (20 IU+3 IU) and a total infusion dose of 23 IU/1000 ml was prepared. Following delivery of the fetus, the placenta was removed and oxytocin was administrated as 2 IU IV bolus in 5-10 seconds. After bolus administration, 23 U/1000 ml oxytocin infusion was started to be administered over 4 hours. The obstetrician assessed uterine tone after removing the placenta and performing uterine massage. Methylergonovine 0.25 mg was administered intramuscular if uterine tone was inadequate.

It was evaluated whether cardiac side effects such as hypotension, tachycardia, arrhythmia, T negativity, ST depression developed after oxytocin bolus administration. Blood pressure and heart rate last measured before oxytocin bolus administration were considered as baseline values and changes were compared with these baseline values. A 20% decrease in blood pressure was considered hypotension and a 20% increase in heart rate was considered tachycardia. The patient was asked about the presence of chest pain and shortness of breath, which are cardiac side effects, and they were evaluated as present or absent.

The presence of symptoms such as nausea-vomiting, headache/type/localisation, flushing, burning sensation on the face, metallic taste on the tongue were evaluated by asking the patient. The type of headache was classified as throbbing, compressive, blunt, and the localisation of headache was classified as frontal, temporal, occipital, and diffuse. Nausea and vomiting, burning sensation, the metallic taste on the tongue were assessed as present or absent. Flushing was evaluated by a clinician as present or absent.

Estimated blood loss was calculated according to the following formula using the haematocrit level at baseline and 4 hours after cesarean; estimated blood loss (mL) = estimated blood volume × (preoperative haematocrit - postoperative haematocrit)/ preoperative haematocrit. The estimated blood volume was calculated as 85.16 ml/kg.

Ethical Approval

The ethics committee approval of this observational drug study was obtained from Selçuk University Faculty of Medicine Clinical Research Ethics Committee (Date: 2020-07-09, No: 2020/17) and Turkish Pharmaceuticals and Medical Devices Agency (20-AKD-103).

Results

803 patients who delivered by cesarean section in our hospital were evaluated. The study included 417 patients who met the inclusion criteria. Demographic data of patients are shown in Table 1. While tachycardia was the most common cardiac side effect with a rate of 42.9%, T-negativity was the least common cardiac side effect with a rate of 1%. Hypotension was observed in 14.6%, chest pain in 10.1% and dyspnea in 5.5% of

417 patients (Table 2). Headache was the most common non-cardiac side effect with a rate of 21.6%. When we classified headache by type, throbbing type (12.5%) and compressive type (7.9%) were the most common; when we classified headache by region, frontal (8.4%) and diffuse headache (7.2%) were the most common. After headache, other common non-cardiac side effects were nausea and vomiting (13.7%), metallic taste on the tongue (9.4%) and burning in the face and ears (8.4%). The other side effects were shown in Table 3. 56 patients needed methylergonovine because of inadequate uterine tone (Table 1).

Table 1. Demographic datas (n=417)

		Mean	SS
Age (year)		29.86	5.61
Weight (kg)		80.9	14.2
Height (cm)		162.9	5.93
BMI (kg/m2)		30.8	5.1
Gravida		2.68	1.37
Number of caesarean sections		1.99	1.36
		n	%
Gestational HT		13	3.1
Gestational DM		33	7.9
Preeclampsia		9	2.2
Uterotonic requirement		56	13.4
Co-morbidity	Asthma	16	3.8
	HT	8	1.9
	Hypothyroid	39	9.4
	DM	8	1.9
	Other	22	5.3

Table 2. Cardiac side effects (n=417)

	n	%
Hypotension	61	14.6
Tachycardia	179	42.9
Chest pain	42	10.1
Dispne	23	5.5
Arrhythmia	18	4.3
T-negativity	4	1
ST depression	11	2.6

Table 3. Non-cardiac side effects (n=417)

		n	%
Nausea and vomiting		57	13.7
Flushing		14	3.4
Burning in the face-ears		35	8.4
Metallic taste on the tongue		39	9.4
Headache		90	21.6
Type	Throbbing	52	12.5
	Compressive	33	7.9
	Blunt	5	1.2
Location	Frontal	35	8.4
	Occipital	16	3.8
	Temporal	9	2.2
	Diffuse	30	7.2

The estimated calculated blood loss was 618.5 ± 326.3 ml.

Discussion

In this study, tachycardia 42.9%, hypotension 14.6%, ST depression 2.6%, T negativity 1%, headache 21.6%, nausea-vomiting 13.7% were observed after 2 IU oxytocin bolus administration.

Oxytocin is the most commonly used uterotonic drug to prevent uterine atony, the most common cause of postpartum bleeding and it has traditionally been used in higher doses. However, recent studies have shown that lower doses may be as effective as higher doses [2, 5, 6]. Many studies over the last two decades have failed to reach a consensus on the ideal dose and route of administration [3, 7]. There is compelling evidence to support the use of a combination of bolus and infusion doses for efficacy and safety. According to a meta-analysis of 37 studies, there was some evidence to recommend 3-5 IU bolus and 0.25-1 IU/min infusion to achieve optimum effects, while there was insufficient evidence for high doses (> 5 IU bolus or infusion ≥ 1 IU/min) [8]. The latest guideline recommends an initial bolus dose of 1 IU and if uterine tone is insufficient after 2 minutes, a 3 IU bolus is recommended [2]. Since there are few studies on 2 IU bolus administration in the literature, we preferred this dose in our study.

Oxytocin has a short half-life as 4-10 minutes and requires continuous intravenous infusion for efficacy [9]. According to pharmacokinetics, the therapeutic plasma concentration of a drug is rapidly achieved by first administering a bolus followed by a maintenance infusion. Therefore, Stephens and Bruessel recommended a bolus dose followed by infusion in their systematic review of oxytocin dosing in cesarean delivery [10]. In a study investigating haemoglobin changes after delivery, 40 IU of oxytocin infused within 30 minutes was found to be as effective as 60 and 80 IU of oxytocin infused in the same period. Duffield et al. infused oxytocin at 2.5 IU/h and 15 IU/h after a 1 IU bolus and showed that increasing infusion doses had no extra contribution to improving tone or reducing blood loss [11]. In our study, our infusion protocol (23 IU / 4 h) was organised according to the doses in the last guideline (2.5-7.5 IU/h) [2]. Oxytocin infusion has been reported to reduce postpartum haemorrhage compared to bolus administration alone, reducing the need for transfusions and additional uteronics. However, the optimal duration of oxytocin infusion after the onset of uterine tone is unknown [2]. In our study, we started infusion immediately after the bolus dose.

Oxytocin-induced hypotension results from vasodilatation mediated by oxytocin receptors in the vascular endothelium, mainly by calcium-dependent stimulation of the nitric oxide pathway. It also leads to a mild negative inotropic effect, probably by modulating acetylcholine release from intrinsic cardiac cholinergic neurones [3]. Butwick et al. reported that hypotension developed approximately 22% after 1 IU bolus and 27% after 3 IU boluses in their study. The reason for the high rates of hypotension in their study compared to our study may be due to the different definitions of hypotension; we defined a 20% decrease from baseline as hypotension, while Butwick et al. defined a 10% decrease as hypotension [5]. First, the rate of administration appears to correlate with the incidence of oxytocin-induced hypotension. In studies in

which 5 U oxytocin was administered as a "rapid" bolus, the incidence of hypotension was found to be 100% [12], whereas the same amount of oxytocin was administered in 15 seconds, the incidence of hypotension was found to be 50% [5]. Farber et al., who administered the same amount of oxytocin within 4 minutes and did not observe hypotension in any patient, pointed out that the rate of administration rather than the dose is important to protect against haemodynamic side effects of oxytocin [13]. The fact that hypotension was observed in our study in which a lower dose was administered more rapidly (5-10 sec) supports the thesis of Farber.

Oxytocin decreases systemic vascular resistance by relaxing vascular smooth muscle and tachycardia is observed as a compensatory response to this decrease. Apart from this reflex response, another cause of tachycardia is that oxytocin affects atrioventriculer conduction and myocardial repolarization through oxytocin receptors in the myocardium [3]. Sartain et al. observed tachycardia in 57.5% of patients when they administered oxytocin 5 IU bolus in 5-10 seconds, while this rate was 27.5% when they administered oxytocin 2 IU bolus. [14]. We administered oxytocin 2 IU in approximately the same amount of time, but our tachycardia rate (42.9%) was higher. This may be related to the infusion of phenylephrine, which had the ability to cause reflex bradycardia in the aforementioned study. The high rate of tachycardia in our study may also be due to the dehydration of the patients due to prolonged fasting (>8 hours). Because of the recommendation that "clear liquid can be drunk until the last 2 hours before the operation" could not be put into routine practice in our hospital.

The effect of oxytocin on the ST segment is dose-dependent. In a randomised study, ST depression occurred in 8% of patients when oxytocin was administered as a 5 IU bolus and in 22% of patients when oxytocin was administered as a 10 IU bolus [15]. In recent years, the dose for PPH prophylaxis has been reduced due to awareness of the transient haemodynamic changes and dose-dependent ST depression following intravenous oxytocin. Rudingwa et al. administered 2.5 IU oxytocin within 1 minute and found ST depression as 4.8% [16]. In this study in which relatively similar doses were administered for a longer period of time, the ST depression rate was found to be higher than the rate in our study. The reason for this may be that they captured ST depression more clearly with holter monitoring. The haemodynamic effects of oxytocin also depend on the route of administration and dose. When 3 IU oxytocin was administered in 15 seconds, ST depression was observed in 7.5% of the patients, whereas no ST depression was observed when the same dose was administered in 5 minutes [17].

While the incidence of headache was 12% in the study in which oxytocin 5 IU bolus was administered [18], it was 28% in the study in which 10 IU bolus was administered [9] and 21.6% in our study. In the study by Bekkenes et al. in which oxytocin 1 IU bolus was administered, the headache rate was found to be very low (4.8%) [16]. In a meta-analysis, headache was reported in 14% (142 of 991) patients [19]. As far as we could reach in the literature, the type of oxytocin-induced headache has not been classified. The majority of headaches were of the throbbing type, followed most frequently by the compressive type. Oxytocin is known to activate the NO pathway in vascular endothelium [20]. Extensive studies have shown that NO is associated with many types of primary headache, including migraine, cluster and tension-type headache [21].

Rabow et al. reported that oxytocin caused global vasodilatation by reducing vascular tone in both large and small arteries [22]. The occurrence of flushing even at low doses is an indication of how potent the drug has a vasodilator effect [23]. In the study comparing 0.5 and 5 IU oxytocin, flushing rates were found to be 17% and 29% respectively [24]. In our study, the rate of flushing was 3.4% and the rate of burning in the face-ears was 8.4%. Although the pathophysiology of both effects is based on vasodilation, the difference in the rates may be due to the fact that the presence of flushing depends on the observation of the investigator and flushing may not be noticeable in dark-skinned patients.

Elbohoty et al. administered oxytocin as 10 IU bolus followed by 20 IU/4 hour infusion and 13% of patients required ergometrine [9]. The bolus dose in this study was 5 times our bolus dose, while our infusion protocol can be considered similar. In another study with 2 times the bolus dose and half the infusion dose in our study (5 IU bolus and 20 IU/10 hour infusion), the rate of additional uterotonic requirement was 16% [24]. Stålberg et al. did not start the infusion immediately but only administered a bolus of 2.5 IU oxytocin and 13.8% needed ergometrine [25]. These results suggest that the main factor determining the need for additional uterotonic is the infusion dose rather than the bolus dose.

Limitation

Further haemodynamic monitoring could have been performed, but we wanted to demonstrate the side effect profile that could be noticed without going beyond the routine monitoring performed in obstetric anaesthesia.

We could have evaluated the duration and severity of the headache.

Conclusion

Cardiac and non-cardiac side effects can be seen even with low dose (2IU) oxytocin administered bolus in 5-10 seconds.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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